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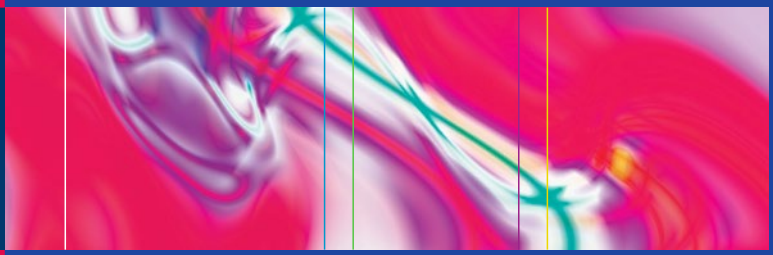

Diabetes and Cardiovascular Disease

A Guide to Clinical Management

Springer

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Foreword

In the current environment, cardiovascular disease continues to be one of the causes – if not the leading cause – of mortality worldwide. Therefore, it is important to have publications and books, which provide appropriate perspective on the clinical management of these conditions. What makes this book timely and clinically relevant is linking it to the ongoing worldwide epidemic of diabetes, which appears to be a major factor for retarding the rate of decline in cardiovascular disease.
This book not only describes the various cardiovascular diseases and pathologies that are particularly predominant in the diabetic population, such as accelerated atherosclerosis, stroke, peripheral vascular disease and cardiomyopathy, but also addresses in a contemporary manner the major risk factors that lead to the increased burden of cardiovascular disorders in individuals with diabetes. Such risk factors include hypertension, thrombosis and dyslipidemia.

The pathogenesis of diabetes-related cardiovascular disorders has not been fully elucidated. The last decade of research has led to an explosion in our knowledge base in the field of diabetes and cardiovascular disease, due to the increasing use of state of the art techniques, including unbiased approaches such as next generation sequencing, increased interest in epigenetic approaches to explore gene/environment interactions, use of animal models to define, at a molecular and biochemical level, important pathways leading to disease, and sophisticated methods to measure lipids, proteins, DNA and RNA in various human samples. If this will lead to new treatments aimed at

preventing or reducing the burden of disease, is still to be determined. However, this book provides a comprehensive and contemporary summary of the current treatments available. This includes anti-thrombotics, lipid lowering drugs, antihypertensive agents, and drugs specifically indicated for heart failure. There is a significant number of controversies in managing the diabetic patient and these are addressed in this book. This includes appropriate use of various anti-platelet agents and the optimal approach to address coronary artery disease in individuals with diabetes. A major issue relates to modern management of glycemic control in the diabetic population. With a dramatic increase in the number of medications available to lower glucose and the requirement by regulatory authorities to assess the impact of new glucose lowering agents on cardiovascular disease and mortality in diabetes, this topic remains an area of active clinical investigation. Furthermore, with the possibility that certain glucose lowering agents may be associated with effects in either increasing or reducing hospitalization for heart failure, the impact of glucose lowering drugs continues to be regularly monitored in the ongoing clinical trials.

Diabetic subjects, though in general at high risk of developing cardiovascular disease, are markedly different in terms of prognosis. It is hoped that identification of biomarkers or use of new vascular imaging approaches will help to identify those at highest risk who would be candidates for more aggressive multifactorial intervention to reduce cardiovascular burden and overt clinical disease. This book addresses the use of various available risk engines as well as providing a balanced summary of the current status of a range of putative biomarkers.

In summary, this practical yet scientifically rigorous book will interest not only clinicians but also researchers who want to learn more about cardiovascular disease in the diabetic population. Since diabetes is a common cause of premature cardiovascular disease, and cardiovascular disease, in turn, is

responsible for more than 60 % of deaths in diabetic subjects, this book will interest cardiologists, endocrinologists (including diabetologists), general physicians and family doctors with a particular interest in diabetes.

With the increased knowledge, better understanding of the complexity of cardiovascular disease in the diabetic patient and improved treatment approaches, it is hoped that over the next decade we will see a further reduction in the burden of cardiovascular disease, particularly in the setting of concomitant diabetes.

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Chapter 1
Epidemiology, Definition, and Diagnosis of Diabetes Mellitus

1.1 Global Burden of Diabetes

The prevalence of metabolic diseases such as obesity and diabetes (DM) is alarmingly increasing over the globe [1, 2]. The main determinants behind this process are represented by modifiable (environment, overnutrition, sedentary habits, smoking) and nonmodifiable factors such as genetic susceptibility and aging [3]. An important aspect to consider is that environmental changes have a strong legacy effect over the next generations [4–6]. In other words, long-term high caloric regimens and physical inactivity are capable to derail gene expression and cellular programs, and these alterations may be transmitted to the offspring thereby anticipating metabolic traits even in young, normoweight individuals [4, 7]. In line with this emerging notion, obesity and prediabetes are exploding in young adolescents and represent a major public health problem [1, 8]. Epidemiological analysis show that 6.9 % of the global population (316 million people) is currently affected by impaired glucose tolerance (IGT) and, most importantly, projections anticipate a dramatic IGT increase with more that 470 million people affected by the year 2035 (Fig. 1.1). Such

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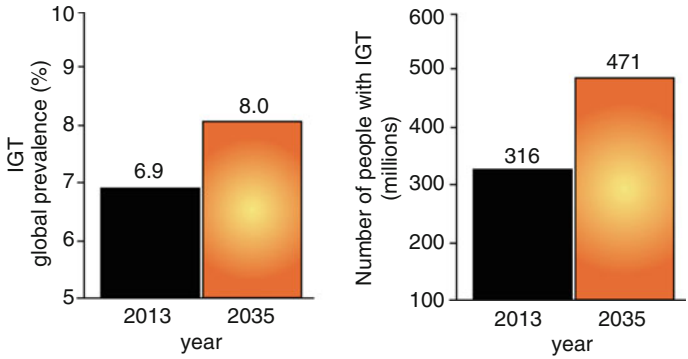

Fig 1.1 Worldwide prevalence of impaired glucose tolerance (Modified from International Diabetes Federation (IDF) [1]). *IGT* impaired glucose tolerance

pandemic of metabolic syndromes and obesity-related disorders hints a proportional increase in the prevalence of type 2 diabetes (T2D). The link between environmental factors, obesity, and subsequent dysglycemia indicates that the progression to DM occurs along a "continuum," not necessarily linear with time, which involves different cellular mechanisms including tissue-specific alterations of insulin signaling, changes in glucose transport, pancreatic beta cell dysfunction as well as deregulation of key genes involved in oxidative stress and inflammation [9–11]. Prevalence of metabolic disorders in adolescents is further boosted by pregnancy-related DM [12, 13]. Indeed, 21 million of live births were affected by DM only in the year 2013, suggesting that uterine environment plays a pivotal role (Table 1.1) [14].

Nowadays, 382 million people are affected by DM worldwide with most of cases registered in Western Pacific (138 million), South East Asia (72 million), and Europe (56 million) (Table 1.2) [1]. The majority of the 382 million people with DM are aged between 40 and 59, and 80 % of them

Table 1.1 Hyperglycemia in pregnancy in women (20–49 years)

Global prevalence (%)	16.9
Comparative prevalence (%)	14.8
Number of live births with hyperglycemia in pregnancy (millions)	21.4
Proportion of cases that may be due to diabetes in pregnancy (%)	16.0

Data from International Diabetes Federation (IDF) [1]

Table 1.2 Global forecasts of the number of people with diabetes from 2013 to 2035

Region	2013 (millions)	2035 (millions)	Increase %
Africa	19.8	41.4	109
Middle-East and North Africa	34.6	67.9	96
South-East Asia	72.1	123	71
South and Central America	24.1	38.5	60
Western Pacific	138.2	201.8	46
North America and Caribbean	36.7	50.4	37
Europe	56.3	68.9	22
World	**381.8**	**591.9**	**55**

Data from International Diabetes Federation (IDF) [1]

live in low- and middle-income countries. Most importantly, in these regions the disease remains largely undiagnosed (Table 1.3). Indeed almost 50 % of the people living in Western Pacific and South East Asia are not aware of the disease and remain undiagnosed for many years, leading to clear delays in the application of prevention and treatment strategies. Estimates by the International Diabetes Federation forecast that 592 million individuals will be affected by DM in 2035 (Table 1.2). This indicates that disease prevalence may increase by 55 % in only 22 years. Interestingly, new cases of DM will be mostly detected in Africa (109.1 %), Middle East and North Africa (96.2 %) as well

Table 1.3 Proportion of undiagnosed cases of diabetes in 2013 (20–79 years)

Region	Undiagnosed cases (%)
Africa	62
South-East Asia	49
South and Central America	24
Western Pacific	54
North America and Caribbean	27
Europe	48

Data from International Diabetes Federation (IDF) [1]

as South East Asia (70.6 %). By contrast, trajectories of DM prevalence are expected to be smoother in developed countries such as North America and Europe (Table 1.2). These differences might be explained by the fact that different forms of the disease are growing over the globe. Type 1 diabetes (T1D) is characterized by reduced pancreatic insulin secretion [15]. Several factors may contribute to T1D, including genetics and exposure to specific viruses triggering altered immune response and subsequent beta cell disruption (Fig. 1.2). Although T1D usually appears during childhood or adolescence, it also can begin in adults. In the latter condition, known as latent auto-immune DM in adults (LADA), insulin dependence develops over a few years.

T2D is a multifactorial disease, generally preceded by a state of overweight and characterized by the combination of insulin resistance (IR), increased free fatty acids (FFAs), and hyperglycemia (Fig. 1.2). Regardless of the underlining causes, DM represents a huge and growing problem with exponential costs for the society. This is particularly true for low-income countries where such DM epidemic will not be affordable by health care systems, with further increase of morbidity and mortality. DM is indeed one of the biggest killers together with cancer and cardiovascular disease, being responsible of 5.1 million death and USD 584 billion dollars expenditures only in the year 2013 [16].

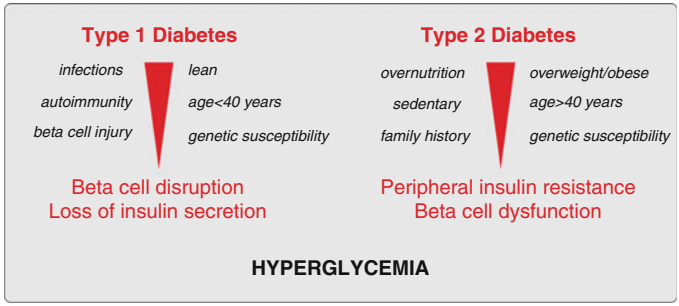

Fig. 1.2 Pathophysiology and risk factors associated with occurrence of type 1 and type 2 diabetes

1.2 Definition

DM is a complex disease characterized by an array of different mechanisms ultimately resulting in elevated blood glucose levels [17]. The disease is associated with high morbidity and mortality due to several complications occurring in multiple organs, including the cardiovascular system (coronary heart disease, peripheral artery disease, heart failure, and stroke). DM also affects the kidneys (diabetic nephropathy), the eyes (retinopathy), the peripheral nervous system (neuropathy), and the limbs (foot ulcers, amputations, Fig. 1.3). Beside these complications, DM increases susceptibility to infections, cancer, cognitive decline, and gastrointestinal disease. T1D is usually diagnosed in children and young adults, and was previously known as juvenile diabetes [18]. Only 5 % of people with DM have this form of the disease [16]. In contrast, patients who develop T2D are generally sedentary and obese. The progression from IGT to T2D may take many years to occur, leading to different intermediate disease phenotypes with continuous changes in glucose parameters and shifts in glucose tolerance category [3, 19]. Hence, understanding the

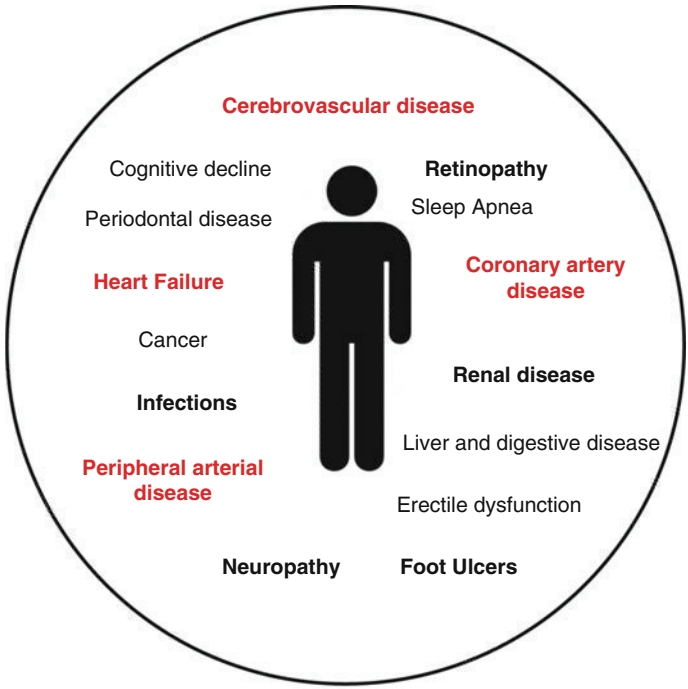

Fig. 1.3 Schematic representing diabetes-related comorbidities

factors predisposing to T2D is a major challenge. A growing form of DM is gestational diabetes which develops during pregnancy [20]. After delivery, most return to a euglycemic state, but they are at increased risk for overt T2D in the future. A meta-analysis reported that subsequent progression to DM is considerably increased after gestational DM. A large Canadian study found that the probability of DM developing after gestational DM was 4 % at 9 months and 19 % at 9 years after delivery [21].

Table 1.4 Cut-points for the diagnosis of impaired fasting glucose (IGF), impaired glucose tolerance (IGT), and diabetes

Condition	Criteria
Diabetes	
HbA_{1c}	≥6.5 % (48 mmol/mol)
FPG	≥7.0 mmol/L (≥126 mg/dL)
2hPG	≥11.1 mmol/L (≥200 mg/dL)
IGT	
FPG	<7.0 mmol/L (<126 mg/dL)
2hPG	7.8–11.0 mmol/L (140–198 mg/dL)
IFG	
FPG	5.6–6.9 mmol/L (100–125 mg/dL)
2hPG	<7.8 mmol/L (<140 mg/dL)

HbA1c glycated hemoglobin, *FPG* fasting plasma glucose, *IFG* impaired fasting glucose, *IGT* impaired glucose tolerance, *2hPG* 2-h plasma glucose

1.3 Diagnosis

In most of cases DM is a silent disease and half of the 382 million individuals with diabetes in 2013 were unaware of their diagnosis. Moreover, 300 million individuals show early features of altered glucose homeostasis, leading to a future risk of developing DM. Despite advances in diagnosis and treatment, we are still far from the identification of a reliable hyperglycemic marker for the detection of DM. DM is generally diagnosed when fasting plasma glucose (FPG) levels are ≥126 mg/dL in two different determinations (Table 1.4). Glycated hemoglobin (HbA_{1c}) has been recently introduced as a diagnostic test in combination with fasting plasma glucose (FPG). HbA_{1c} is indeed a simple marker which may accurately reflect a condition of chronic hyperglycemia or altered glucose homeostasis [22]. However, there remain concerns regarding its sensitivity in